

Exhibit E

ADVANCED ORGANIC CHEMISTRY

1966

Structure

Reaction

Jerry March

ADVANCED ORGANIC CHEMISTRY

REACTIONS,
MECHANISMS, AND
STRUCTURE

FOURTH EDITION

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Adelphi University



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An aldehyde or ketone is treated with an α -halo ester (e.g., α -halo ketones,⁴⁴³ α -halo N,N-disubstituted acids⁴⁴⁴ have also been used. With especially high reactivity can be achieved and with zinc and ultrasound.⁴⁴⁷ The use of zinc (e.g., In,⁴⁴⁸ Mn⁴⁴⁹) and Te,⁴⁵¹ and Bu₃Sb.⁴⁵² The aldehyde or ketone contains various functional groups. HF, and 1,4-dioxane.

The reaction is analogous to the Grignard reaction and to RMgX. There is an

structure of which has been shown to be prepared from *t*-BuOCOCH₂Br and

t -Bu

of 32.

but sometimes (especially with aryl ketones) is an olefin. By the use of Bu₃P, making this an alternative to the Reformatsky reaction, α -halo esters, ketones and yields are sometimes been carried out on nitriles.⁴⁵⁵

act. 1975, 22, 423-460; Gaudemar *Organomet.*

56, 2659; Palomo; Aizpurua; López; Aurremunt. 1990, 20, 3277.
see Huang; Chen; Shen *J. Chem. Soc., Perkin* 1985, 26, 4371.

1. 1991, 21, 133.

75. See also Bortolussi; Seyden-Penne *Synth.*

Synth. Commun. 1988, 18, 453.

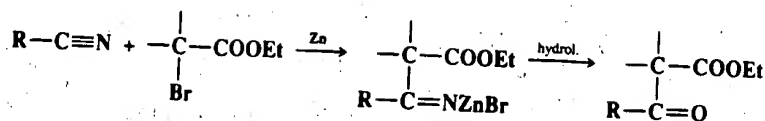
awamura; Inanaga; Yamaguchi *Tetrahedron* 1984, 3, 1403.

1984, 3, 1403.

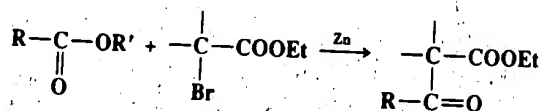
method. see Huang; Shi; Li; Wen *J. Chem.*

associated; Gaudemar *J. Organomet. Chem.*

REACTION 6-31

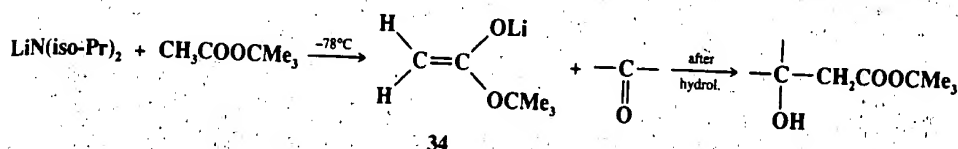


Carboxylic esters have also been used as substrates, but then, as might be expected (p. 881), the result is substitution and not addition:



The product in this case is the same as with the corresponding nitrile, though the pathways are different.

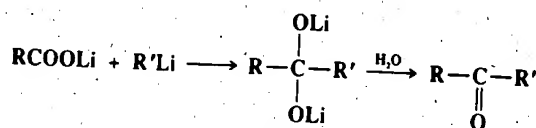
Addition of *t*-butyl acetate to lithium diisopropylamide (LDA) in hexane at -78°C gives the lithium salt of *t*-butyl acetate⁴⁵⁶ (2-22) as a stable solid. The nmr and ir spectra of this



salt in benzene show it to have the enolate structure 34. Reaction of 34 with a ketone provides a simple rapid alternative to the Reformatsky reaction as a means of preparing β -hydroxy *t*-butyl esters. A similar reaction involves treatment of a ketone with a silyl ketene acetal $R_2C=C(OSiMe_3)OR'$ in the presence of $TiCl_4$ ⁴⁵⁷ (see also the reaction between silyl enol ethers and aldehydes and ketones, in 6-39).

OS III, 408; IV, 120, 444.

6-31. The Conversion of Carboxylic Acid Salts to Ketones with Organometallic Compounds Alkyl-de-oxido-substitution



Good yields of ketones can often be obtained by treatment of the lithium salt of a carboxylic acid with an alkyl lithium reagent, followed by hydrolysis.⁴⁵⁸ R' may be aryl or primary, secondary, or tertiary alkyl. MeLi and PhLi have been employed most often. R may be

⁴⁵⁶Rathke; Sullivan *J. Am. Chem. Soc.* 1973, 95, 3050.

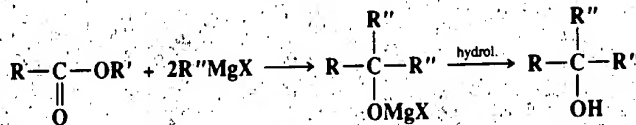
⁴⁵⁷See for example, Saigo; Osaki; Mukaiyama *Chem. Lett.* 1975, 989; Palazzi; Colombo; Gennari *Tetrahedron Lett.* 1986, 27, 1735; Oppolzer; Marco-Contelles *Helv. Chim. Acta* 1986, 69, 1699; Hara; Mukaiyama *Chem. Lett.* 1989, 1909. For a list of references, see Ref. 64, pp. 885-887. For methods of preparing silyl ketene acetals, see Revis; Hilty *Tetrahedron Lett.* 1987, 28, 4809, and references cited therein.

⁴⁵⁸For a review, see Jorgenson *Org. React.* 1970, 18, 1-97. For an improved procedure, see Rubottom; Kim *J. Org. Chem.* 1983, 48, 1550.

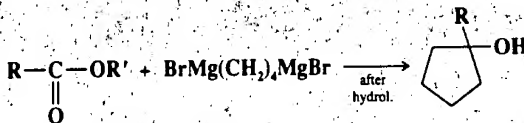
alkyl or aryl, though lithium acetate generally gives low yields. Tertiary alcohols are side products.

OS V, 775.

6-32 The Addition of Grignard Reagents to Acid Derivatives

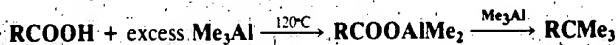


When carboxylic esters are treated with Grignard reagents, there is usually concomitant addition to the carbonyl (6-29) and substitution of R' for OR' (0-104), so that tertiary alcohols are formed in which two R-groups are the same. Formates give secondary alcohols and carbonates give tertiary alcohols in which all three R groups are the same: $(\text{EtO})_2\text{C}=\text{O} + \text{RMgX} \rightarrow \text{R}_3\text{COMgX}$. Acyl halides and anhydrides behave similarly, though these substrates are employed less often.⁴⁵⁹ There are many side reactions possible, especially when the acid derivative or the Grignard reagent is branched: enolizations, reductions (not for esters, but for halides), condensations, and cleavages, but the most important is simple substitution (0-104), which in some cases can be made to predominate. When 1,4-dimagnesium compounds are used, carboxylic esters are converted to cyclopentanols.⁴⁶⁰

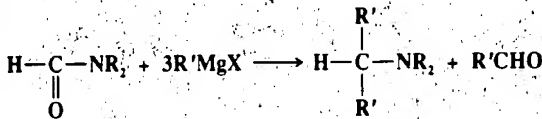


1,5-Dimagnesium compounds give cyclohexanols, but in lower yields.⁴⁶⁰

Trimethylaluminum, which exhaustively methylates ketones (6-29), also exhaustively methylates carboxylic acids to give *t*-butyl compounds⁴⁶¹ (see also 0-90):



Disubstituted formamides can give addition of 2 moles of Grignard reagent. The products of this reaction (called *Bouveault reaction*) are an aldehyde and a tertiary amine.⁴⁶² The use



of an amide other than a formamide can give a ketone instead of an aldehyde, but yields are generally low. It has proven possible to add two different R groups by sequential addition

*For a review of these reactions, see Kharasch; Reinmuth, Ref. 351, pp. 549-766, 846-869

^{44a}Canonne; Bernatchez *J. Org. Chem.* **1986**, *51*, 2147; **1987**, *52*, 4025

⁴¹Meisters: *Mole Aust. J. Chem.* **1974**, *27*, 1665.⁴²For a review, see Ref. 176, pp. 59-63.